PROBLEMS WITH PLATELET INHIBITORS OF THROMBUS FORMATION IN STENOSED DOG CORONARY ARTERIES

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Platelet inhibitory drugs (PID) given to patients or animal models with stenosed coronary arteries (SCA) and thrombosis give mixed results. In our animal model of mechanical SCA with intimal damage, acute platelet thrombus formation (APTF) periodically occurs, producing cyclical coronary flow reductions (CFR's) and ischemia. In 25 open-chest dogs (D) with SCA of 70% diameter reduction, known PID's; 5 mg/kg of aspirin (n=10), 2 mg/kg of the 5HT antagonist, Retanserin (n=5), 5 mg/kg of a thromboxane synthetase inhibitor U63557A (n=5) or 0.4 mg/kg of Dr. Coller's antibody, 7E3, to the platelet GIIb-IIIa receptor (n=5), abolished CFR's in all D. However, epinephrine (E) 0.4 µg/kg/min given IV for 20 min restored CFR's temporarily in 17 of 25 D, but in no 7E3 D, until the E was metabolized. In the same 25 D when CFR's had disappeared after the E infusion the stenosis was increased from 70% to 85-90% decreasing control coronary flow by 30-45%, CFR's reoccurred in 18 of the 25 D, but in none of the 7E3 D. The PID's used allow E to activate the platelets temporarily, possibly by Ca^{++} mobilization, and ultimately exposing the GIIb-IIIa receptor and permit APTF to reoccur. It is postulated that increased shear forces on platelets with the increased stenoses may alter the membrane and expose GIIb-IIIa receptors directly allowing for renewal of APTF in spite of PID treatment. This is supported by the complete protection of the 7E3 group of D from E infusions or increased stenosis.

It is thought that plaque rupture or vasospasm superimposed on a fixed coronary lesion may acutely increase the degree of stenosis in patients with SCA, increasing the velocity and shear forces on the platelets. Patients with SCA taking PID's may be clinically stable with a 70% stenosis but any mechanism which acutely increases the amount of stenosis, alone or in combination with elevated plasma E may initiate a thrombotic occlusion, and they would not be protected with current antithrombotic therapy.

EFFECTS OF DOPAMINE ON LEFT VENTRICULAR MECHANICS AND ENERGETICS: IMPORTANCE OF DIFFERENTIAL RECEPTOR ACTIVATION

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Dopamine [DA] activates β_1,α_1 and DA receptors in a dose dependent manner. To determine the differential effects of low (2mg/kg/min) vs high (6 mg/kg/min) dose DA on LV mechanics and energetics, 7 pts with dilated cardiomyopathy (age = 45±9 yrs) were studied. LV minor and long axes as well as geometric factor [GF] were determined by echo. LV/AO microtip catheters were used to calculate developed pressure [DP]. Data included myocardial oxygen consumption [MVO_2] (coronary sinus catheter) and LV circumferential wall stress [WS]. Wall stress was calculated at end-diastole ([ED], preload), at end-systole ([ES], afterload) and thruout ejection ([$\int$ WS], systolic load). Contractility [CONT] was measured as deviation from LV ESWS - rate corrected Vcf line generated over a wide range of loads. Values are percent change from baseline. (*p<0.05 vs control)

	HR	PRE-LOAD	AFTER LOAD	DP	GF	$\int$ WS	CONT	MVO_2
DA_2	-4	-26*	-14*	5	-9*	-8*	+ *	-10*
DA_6	+4	-14	0	22*	-13*	+8	++ *	+23*

Thus, (1) Low dose dopamine activates DA and β_1 receptors leading to + preload, afterload, GF and systolic load in conjunction with a mild + in contractility. The energetic cost of the + inotropy was more than offset by the + systolic load resulting in a fall in MVO_2.

(2) High dose dopamine activates DA and α_1 receptors in addition to a more potent β_1 effect. The marked + in contractility was not counterbalanced by a + in HR or systolic load resulting in an unopposed increase in MVO_2.

(3) A drug can result in a spectrum of energetic costs depending on its dose related receptor activation.

Wednesday, March 21, 1990
4:00PM-5:00PM, Room 36
Cardiovascular Functions and Neurohormones

EFFECT OF INTRACORONARY ACETYLCHOLINE INFUSION ON CORONARY DIAMETER IN HYPERTENSIVE PATIENTS WITH ANGINA.

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To study potential mechanisms of angina in hypertensive patients, we examined the integrity of endothelium-dependent vasomotion by comparing the effects of intracoronary acetylcholine (Ach) and nitroglycerin (NTG) in 5 hypertensive (HT) patients and 4 normotensive (NT) controls. All had angiographically normal coronary arteries. All cardioactive medications were withheld >20 hours. Ach (15 and 30 ug/min) was infused into the left anterior descending artery (LAD) followed by NTG 200 ug. LAD diameter was measured from the digital angiogram using an automated edge-detection system and the angiographic catheter as a reference measurement.

During Ach infusion, LAD diameter decreased by 46% from 2.5 +/- 0.3 mm to 1.4 +/- 0.9 in the HT group (p<0.05) compared to a decrease of only 7% from 2.9 +/- 0.7 to 2.7 +/-.8 in the NT group (p<0.05). Preliminary data from 6 pts using intracoronary Doppler indicated a similar decline in flow velocity during Ach in the HT group. Mean arterial pressure and heart rate did not change in either group with Ach. With NTG, the LAD dilated normally in both the HT and the NT group (to 2.6 +/- .4 vs. 3.0 +/- .7).

Thus, symptomatic patients with hypertension demonstrate abnormal coronary vasomotion in response to Ach suggesting impaired endothelium-dependent vasomotion as a mechanism contributing to angina.

EFFECT OF ACUTE ANGIOTENSIN CONVERTING ENZYME INHIBITION ON LEFT VENTRICULAR DIASTOLIC FILLING IN PATIENTS WITH CONGESTIVE HEART FAILURE: RELATION TO RIGHT VENTRICULAR VOLUME

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We examined the effect of angiotensin convening enzyme (ACE) inhibition on LV filling, postulating that this effect is influenced by RV volumes due to ventricular interdependence. In 43 patients with congestive heart failure due to LV systolic dysfunction, radionuclide ventriculography was performed before and 30 minutes after administration of 1.25 mg intravenous enalaprilat. Enalaprilat reduced LV end-systolic volume (112 ± 39 to 107 ± 37 ml/m2; mean ± SD; p<0.05) and increased LV ejection fraction slightly (0.24 ± 0.06 to 0.25 ± 0.06; p<0.05). For the entire patient group, enalaprilat did not alter mean LV peak filling rate (PFR). However, for individual patients, the effect of enalaprilat on PFR was related to baseline RV end-diastolic volume (EDV) (p=0.05) and RV end-systolic volume (p=0.02). This effect was unrelated to LV volumes or ejection fraction. Enalaprilat caused an increase in PFR in patients with RV dilatation but not in patients with normal RV volumes:

Patients with:	RVEDV < 120 ml/m2		RVEDV >= 120 ml/m2	
	Baseline	Enalaprilat	Baseline	Enalaprilat
PFR (EDV/s)	1.72 ± 0.8	1.60 ± 0.8	1.38 ± 0.6	1.71 ± 0.6
PFR (ml/s/m2)	211 ± 83	203 ± 84	244 ± 131	297 ± 162

Conclusions: Enalaprilat effect on LV diastolic filling is related to RV volume but not to LV volume. Enalaprilat augments PFR in patients with RV dilatation but not in patients with normal RV volumes. This finding suggests that a dilated RV impedes LV filling through ventricular interdependence, and this effect is ameliorated by ACE inhibition.